Factor Xa Inhibitor Drug Class Review

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Apixaban (Eliquis®)
Fondaparinux (Arixtra®)
Rivaroxaban (Xarelto®)

Final Report
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Table of Contents

Executive Summary

Introduction: Many anticoagulant drug therapies are available including vitamin K inhibitors, direct thrombin inhibitors, and factor Xa inhibitors. Three factor Xa inhibitors are currently available for use in the United States: apixaban, fondaparinux, and rivaroxaban. Apixaban and rivaroxaban are available as oral tablets and fondaparinux is a subcutaneous injection. Apixaban is dosed twice daily and rivaroxaban should be taken with food. Labeled indications vary between the agents.

The American Heart Association and American Stroke Association recommended the use of an anticoagulant to prevent stroke in patients with AF and list apixaban and rivaroxaban as efficacious alternatives to warfarin or aspirin in patients requiring anticoagulation for stroke prevention. The American College of Chest Physicians recommend a low-molecular-weight heparin (LMWH) for DVT/PE *prophylaxis* in patients undergoing hip or knee replacement surgery. Apixaban, fondaparinux, and rivaroxaban are listed as alternatives. The guidelines recommend initial therapy with a parenteral anticoagulant (preferably LMWH or fondaparinux) followed by VKA for *treatment* of a DVT of the leg or PE.

Clinical Efficacy: The factor Xa inhibitors are not directly compared in any clinical trials. A number of trials comparing the factor Xa inhibitors to warfarin, enoxaparin, aspirin, or placebo are available for evaluation. The majority of this comparative clinical evidence suggests noninferiority or superiority for apixaban, rivaroxaban or fondaparinux compared to the other anticoagulant agents. Safety appears to be similar across treatment groups. Differences in safety or efficacy reported in the clinical trials were clinically similar.

Adverse Drug Reactions: Factor Xa inhibitor therapy is well tolerated and the most common adverse event reported with the agents is bleeding. Black box warnings for increased risk of stroke upon discontinuation of therapy and increased risk for developing epidural or spinal hematomas with concurrent spinal anesthesia are listed with the factor Xa inhibitors. There is no specific reversal agent for the factor Xa inhibitors.

Summary: The factor Xa inhibitors are indicated in the treatment and prevention of VTE and in the prevention of stroke or embolism in patients with nonvalvular atrial fibrillation (AF). Labeled indications vary between the agents. The factor Xa inhibitors appear to have similar rates of safety and efficacy compared to other anticoagulant therapies. Overall, selection of an anticoagulant therapy or factor Xa inhibitor should be based on labeled indications and patient specific characteristics (age, weight, comorbidities, etc.).

Introduction

Several anticoagulant drug therapies are currently available for use in the United States: vitamin K inhibitors, direct thrombin inhibitors, and factor Xa inhibitors. Table 2 provides a summary of the anticoagulant drug classes. This review will focus on the factor Xa inhibitors. Three factor Xa inhibitors are currently available for use in the United States: apixaban, fondaparinux, and rivaroxaban.[1-5] Table 1 compares these agents. Apixaban is an oral tablet dosed twice daily and is indicated in the prevention of embolism in patients with nonvalvular atrial fibrillation.[2] Fondaparinux is supplied as a subcutaneous injection dosed once daily and is indicated in the prevention or treatment of pulmonary embolism (PE) and deep vein thrombosis (DVT).[1] Rivaroxaban is an oral tablet dosed once daily with food and is indicated in the prevention of embolism in patients with nonvalvular atrial fibrillation and in the prevention or treatment of PE and DVT.[3] This review will focus on only the labeled indications for the individual factor Xa inhibitors.

Table 1. Comparison of the Factor Xa Inhibitors[1-5]

Agents	How supplied	Labeled Indications	Unlabeled Indications	Generic
Apixaban (Eliquis®)	Oral tablet: 2.5 mg, 5 mg	Reduce the risk of stroke and embolism in patients with nonvalvular atrial fibrillation	Reduce the risk of recurrent DVT and/or PE	No
Fondaparinux (Arixtra®)	Injection, solution: 2.5 mg/0.5 mL 5 mg/0.4 mL 7.5 mg/0.6 mL 10 mg/0.8 mL	Prophylaxis of DVT in patients undergoing surgery for hip replacement, knee replacement, hip fracture, abdominal surgery in patients > 50 Treatment of acute PE or DVT	Prophylaxis/treatment of DVT in patients with HIT or symptomatic superficial vein thrombosis	Yes
Rivaroxaban (Xarelto®)	Oral tablet: 10 mg, 15 mg, 20 mg	Prophylaxis of DVT in patients undergoing hip or knee replacement surgery Treatment of DVT or PE Reduce the risk of stroke and embolism in patients with nonvalvular atrial fibrillation	N/A	No

Key: DVT = of deep vein thrombosis, PE = pulmonary embolism, HIT = heparin-induced thrombocytopenia

Disease Overview

Cardiovascular diseases are the most common causes of death in the United States and are rapidly growing problems throughout the world.[6-15] Diseases included in this category are ischemic coronary heart disease, stroke, and peripheral arterial disease. A sedentary lifestyle, unhealthy diet, tobacco use, and alcohol abuse are some of the risk

factors for developing a cardiovascular disease. According to the American Heart Association, each day over 2000 Americans will die of a cardiovascular disease (averaging one death every 39 seconds) and each year nearly 800,000 Americans will experience a stroke (averaging one cerebrovascular death every 40 seconds). Therapeutic approaches to prevent cardiovascular disease include lifestyle modification (weight reduction, physical activity, smoking cessation), blood pressure control, lipid-lowering treatment, and use of antiplatelet and antithrombotic agents.[6-12] Previously, the vitamin K antagonist (VKA), warfarin, was the only oral anticoagulant drug available for clinical use and a large body of evidence demonstrating its efficacy in the primary and secondary prevention of thromboembolic events is available.[16] More recently, advances in the development of oral anticoagulant therapies have occurred and three new oral anticoagulants are available: dabigatran (Pradaxa®, direct thrombin inhibitor), apixaban (Eliquis®, factor Xa inhibitor) and rivaroxaban (Xarelto®, factor Xa inhibitor). Labeled indications and dosing varies between the new agents. Table 2 provides a summary of all available anticoagulant drug classes and Table 3 provides specific dosing recommendations for the factor Xa inhibitors.

Prevention of Stroke

Atrial fibrillation (AF) is an arrhythmia characterized by rapid, unpredictable contractions of the atria of the heart.[13-15] Fibrillation of the heart allows blood to pool and increases the risk for clot formation and stroke. AF occurs more frequently with increasing age and about 5% of all people over the age of 65 have AF. AF also occurs more frequently in people with hypertension, congestive heart failure and lung disease. Over 70% of strokes that occur in people with AF will result in death. Treatments available for AF include therapies which restore normal heart rate and anticoagulants to reduce the risk of clot formation.[13-15] Apixaban and rivaroxaban are two oral factor Xa inhibitors indicated in the prevention of stroke in patients with AF. The most recent guidelines from the American College of Cardiology/American Heart Association for the Management of Patients with Atrial Fibrillation (2006, 2011 update)[17-19] do not mention the factor Xa inhibitors for use in patients with AF. The American College of Chest Physicians recently published evidence-based guidelines on Antithrombotic Therapy for Atrial Fibrillation (2012).[20] The guidelines state the preferred choice for anticoagulation is an oral anticoagulant, but do not specify a preferred agent. The American Heart Association and American Stroke Association published a Science Advisory for Healthcare Professionals on Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation in 2012.[21] The advisory recommended the use of an anticoagulant to prevent stroke in patients with AF. According to the advisory, apixaban and rivaroxaban are efficacious alternatives to warfarin or aspirin in patients requiring anticoagulation for stroke prevention.

Treatment and Prevention of DVT/PE

Venous thromboembolism (VTE) refers to a group of diseases characterized by inappropriate coagulation. Deep vein thrombosis (DVT) is the formation of a clot in a deep vein of the body.[13-15] Pulmonary embolism (PE) is the blockage of a pulmonary

artery with a clot which may have originated as a DVT. Risk factors for developing a DVT or PE include major surgery, cancer diagnosis, pregnancy, smoking, overweight, estrogen therapy, family history and older age. The risk of DVT is increased by 42-57% in patients undergoing hip replacement surgery, 41-85% in patients undergoing knee replacement surgery and up to 70% in patients diagnosed with cancer. Anticoagulant therapy may be indicated in the treatment and prevention of VTE disease.[13-15] Fondaparinux (administered subcutaneously) and rivaroxaban (oral tablet) are indicated in the treatment and prevention of DVT and PE. The American College of Chest Physicians recently published evidence-based guidelines on Antithrombotic Therapy for Antithrombotic Therapy and Prevention of Thrombosis (2012).[16, 22-24] The guidelines suggest the use of low-molecular-weight heparin (LMWH) for DVT/PE prophylaxis in patients undergoing hip or knee replacement surgery. Apixaban, fondaparinux, and rivaroxaban are listed as alternatives. Fondaparinux is listed as a preferred agent for DVT/PE prophylaxis in patients undergoing hip fracture surgery. In patients undergoing hip or knee replacement surgery who refuse LMWH injections or an intermittent pneumatic compression device (IPCD), prevention with apixaban or dabigatran may be used. For treatment of a DVT of the leg or PE, initial therapy with a parenteral anticoagulant (preferably a LMWH or fondaparinux) followed by warfarin is recommended.

Table 2. Summary of Anticoagulant Drug Therapies[4, 5]

Drug	Route	Mechanism of action	Metabolism	Monitoring	Clinical features	Generic
Apixaban (Eliquis®)	Oral	Directly inhibits factor Xa	CYP3A4 P-glycoprotein substrate *Not recommended in severe liver insufficiency	Routine lab monitoring not required Reversal: No antidote; **not** dialyzable	Indicated in the reduction of stroke and embolism in patients with nonvalvular atrial fibrillation Compliance may be a problem (twice daily dosing) Dose adjustment required in renal insufficiency (Cl_{Cr}<25 mL/min) U.S. Boxed Warning: An increased risk of stroke may occur upon discontinuation Drug interactions Half-life ~8-15hrs; hold 24-48 hrs before surgery	No
Argatroban	Intravenous	Directly inhibits thrombin	Hepatic via hydroxylation and aromatization. Metabolism via CYP3A4/5 to four known metabolites plays a minor role.	aPTT required	Indicated in the prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT) Dose adjustment required in hepatic insufficiency May be used in pediatrics Half-life ~ 39-51 minutes; hepatic impairment: ≤181 minutes; hold before surgery	Yes
Bivalirudin (Angiomax®)	Intravenous	Directly inhibits thrombin	Blood proteases	ACT or aPTT required	Indicated in conjunction with aspirin for patients with unstable angina undergoing percutaneous coronary intervention (PCI) Dose adjustment required in renal insufficiency Half-life ~ 25 minutes (normal renal function) to 57 minutes (renal impairment) to 3.5 hours (on dialysis); hold before surgery	No

Drug	Route	Mechanism of action	Metabolism	Monitoring	Clinical features	Generic
Dabigatran (Pradaxa®)	Oral	Directly inhibits thrombin	Hepatic glucuronidation P-glycoprotein substrate	Routine lab monitoring not required Reversal: No antidote (4-factor PCC **not** effective); 60% dialyzable	Indicated in the reduction of stroke and embolism in patients with nonvalvular atrial fibrillation Compliance may be a problem (twice daily dosing) Dose adjustment required in renal insufficiency (*contraindicated in Cl_{Cr}<30 mL/min) Use with extreme caution in patients aged ≥80 U.S. Boxed Warning: Upon discontinuation, the risk of thrombotic events, especially stroke, is increased Drug interactions Half-life ~12-17hrs; may consider holding >5 days before surgery	No
Dalteparin (Fragmin®)	Subcutaneous Intravenous	LMWH; Inhibits both factor Xa and factor IIa	Hepatic	Routine lab monitoring not required; anti-Xa levels may be used to monitor efficacy Reversal: No antidote; protamine may be used for partial reversal	Indicated in the prevention of deep vein thrombosis (DVT) Dosing frequency varies with indication May require weight-based dosing Dose adjustment required in renal insufficiency Contraindicated in patients with current heparin-induced thrombocytopenia (HIT) U.S. Boxed Warning: Spinal or epidural hematomas may occur with neuraxial anesthesia in patients anticoagulated with LMWH Half-life ~2-5hrs; hold ≥24 hours before surgery	No

Drug	Route	Mechanism of action	Metabolism	Monitoring	Clinical features	Generic
Desirudin (Iprivask®)	Subcutaneous	Directly inhibits thrombin	Renal; 40-50% of dose excreted unchanged	aPTT required	Indicated in the treatment and prevention of DVT/PE Do not administer I.M. U.S. Boxed Warning: Spinal or epidural hematomas may occur with concurrent neuraxial anesthesia Dose adjustment required in renal insufficiency Half-life ~2hrs	No
Enoxaparin (Lovenox®)	Subcutaneous	LMWH; Inhibits both factor Xa and factor IIa	Hepatic	Routine lab monitoring not required; anti-Xa levels may be used to monitor efficacy Reversal: No antidote; protamine may be used for partial reversal	Indicated in the treatment of acute coronary syndromes and the treatment and prevention of DVT/PE Compliance may be a problem Dosing frequency varies with indication May be used in pregnancy May require weight-based dosing Dose adjustment required in renal insufficiency Drug interactions Contraindicated in patients with current heparin-induced thrombocytopenia (HIT) U.S. Boxed Warning: Spinal or epidural hematomas may occur with neuraxial anesthesia in patients anticoagulated with LMWH Pregnancy Risk Factor B Guidance available for use in pediatric patients Half-life ~4.5-7hrs; hold $\geq$24 hrs before surgery	Yes

Drug	Route	Mechanism of action	Metabolism	Monitoring	Clinical features	Generic
Fondaparinux (Arixtra®)	Subcutaneous	Directly inhibits factor Xa	Eliminated unchanged in urine	Routine lab monitoring not required Reversal: No antidote; 20% dialyzable	Indicated in the treatment or prevention of PE or DVT Do not administer I.M. May require weight-based dosing Dose adjustment required in renal insufficiency U.S. Boxed Warning: Spinal or epidural hematomas, including subsequent paralysis, may occur with neuraxial anesthesia Pregnancy Risk Factor B Half-life ~17-21hrs; hold 2-3 days before surgery	Yes
Rivaroxaban (Xarelto®)	Oral	Directly inhibits factor Xa	CYP3A4, 3A5, 2J2 P-glycoprotein substrate	Routine lab monitoring not required Renal and liver monitoring required Reversal: No antidote; **not** dialyzable	Indicated in the reduction of stroke and embolism in patients with nonvalvular atrial fibrillation and the treatment or prevention of PE or DVT Administer with food Dosing frequency varies with indication Dose adjustment required in renal insufficiency Use with caution in hepatic insufficiency U.S. Boxed Warning: An increased risk of stroke was noted upon discontinuation of rivaroxaban in clinical trials of patients with atrial fibrillation U.S. Boxed Warning: Spinal or epidural hematomas, including subsequent paralysis, may occur with neuraxial anesthesia Drug interactions Half-life ~5-9hrs; hold ≥24 hours before surgery	No

Drug	Route	Mechanism of action	Metabolism	Monitoring	Clinical features	Generic
Warfarin (Coumadin®)	Oral	Inhibits the formation of vitamin K-dependent clotting factors (II, VII, IX, X, and proteins C and S)	CYP2C9, 1A2, 3A4, 2C19	PT/INR required Reversal: Vitamin K, PCC, FFP	Indicated in the prophylaxis and treatment of thromboembolic disorders and as an adjunct to reduce risk of systemic after myocardial infarction Drug **and** food interactions Full therapeutic effect seen ~5-7 days U.S. Boxed Warning: May cause major or fatal bleeding Labeled for use in pediatrics Half-life ~40hrs; hold for at least 5 days before surgery	Yes

Key: PCC = prothrombin complex concentrate, FFP = fresh frozen plasma, LMWH = low molecular weight heparin

Table 3. Dosing of the Factor Xa Inhibitors[1-5]

Agents	Available doses	Dosing	Conversion instructions	Notes
Apixaban (Eliquis®)	Oral tablet: 2.5 mg, 5 mg	Usual dose: Nonvalvular atrial fibrillation: 2.5- 5 mg twice daily (age ≥80 yrs, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL use reduced dose of 2.5 mg Max dose: 10 mg/day	Conversion from warfarin to apixaban: Discontinue warfarin and initiate apixaban when INR is <2.0 Conversion from apixaban to warfarin: discontinue apixaban and begin both a parenteral anticoagulant with warfarin and discontinue parenteral anticoagulant when INR reaches an acceptable range. Conversion between apixaban and other non-warfarin anticoagulants: Discontinue anticoagulant being taken and begin the other at the next scheduled dose.	Dosage adjustment is required with strong CYP3A4 and P-glycoprotein inhibitors (eg, clarithromycin, ketoconazole, itraconazole, ritonavir): 2.5 mg twice daily Apixaban affects the INR
Fondaparinux (Arixtra®)	Injection, solution: 2.5 mg/0.5 mL 5 mg/0.4 mL 7.5 mg/0.6 mL 10 mg/0.8 mL	Usual dose: DVT prophylaxis: SubQ: Adults ≥50 kg: 2.5 mg once daily. Acute DVT/PE treatment: Start fondaparinux and warfarin on the first or second treatment day and continue fondaparinux until INR is ≥2 for at least 24 hours (usually 5-7 days) <50 kg: 5 mg once daily 50-100 kg: 7.5 mg once daily >100 kg: 10 mg once daily Max dose: 10 mg/day	Discontinue fondaparinux 24 hours prior to CABG surgery and administer unfractionated heparin	Usual duration for prophylaxis or treatment: 5-9 days *The American College of Chest Physicians recommends a minimum of 10-14 days of prophylaxis in patients undergoing total hip, total knee or hip fracture surgery
Rivaroxaban (Xarelto®)	Oral tablet: 10 mg, 15 mg, 20 mg	Usual dose: Treatment of DVT and PE: 15 mg twice daily with food for 3 weeks followed by 20 mg once daily with food. Reduction in the risk of recurrent DVT/PE: 20 mg once daily with food; duration of treatment 6-24 months	Conversion from warfarin: Discontinue warfarin and initiate rivaroxaban as soon as INR falls to <3.0 Conversion to warfarin: 24 hours after discontinuation of rivaroxaban begin both a parenteral anticoagulant with warfarin and discontinue parenteral anticoagulant when INR reaches an acceptable range.	Extremes of body weight (<50 kg or >120 kg) do not influence rivaroxaban dose Clinical out Rivaroxaban affects INR

Agents	Available doses	Dosing	Conversion instructions	Notes
		Prevent stroke and/or embolism: 20 mg once daily with the evening meal. Postoperative thromboprophylaxis: 10 mg once daily; recommended total duration of therapy for 12-14 days <u>Max dose:</u> 30 mg/day	Conversion from continuous infusion unfractionated heparin: Initiate rivaroxaban at the time of heparin discontinuation Conversion to continuous infusion unfractionated heparin: Initiate continuous infusion unfractionated heparin 24 hours after discontinuation of rivaroxaban Conversion from other anticoagulants: Discontinue current anticoagulant and initiate rivaroxaban ≤2 hours prior to the next dose Conversion to other anticoagulants (other than warfarin): Initiate the anticoagulant 24 hours after discontinuation of rivaroxaban	

Key: CABG = coronary artery bypass graft

Pharmacology/Pharmacokinetics[1-5]

Fondaparinux is a synthetic form of the antithrombin-binding pentasaccharide sequence of heparin and LMWH and inhibits platelet activation and fibrin clot formation via antithrombin.

Apixaban and rivaroxaban inhibit free and clot-bound factor Xa which results in inhibition of the conversion of prothrombin to thrombin and inhibition of platelet activation and fibrin clot formation.

Table 4. Pharmacokinetics of the Factor Xa Inhibitors[1-3]

Agents	Absorption	Distribution	Half-life	Time-to-peak	Metabolism	Excretion
Apixaban (Eliquis®)	Onset: 3-4 hours Bioavailability: ~50%	Vd: ~21 L Protein binding: ~87%	2.5 mg: ~8 hours 5 mg: ~15 hours	3-4 hours	Hepatic predominantly via CYP3A4/5 to inactive metabolites *substrate of P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP)	Urine (~27% as parent drug); feces (~25% of dose recovered as metabolites)
Fondaparinux (Arixtra®) [preservative free]	SubQ: Rapid and complete Bioavailability: SubQ: 100%	Vd: 7-11 L; mainly in blood Protein binding: ≥94% to antithrombin III	17-21 hours *prolonged with renal impairment	SubQ: 2-3 hours	Eliminated unchanged in urine	Urine (~77%, unchanged drug)
Rivaroxaban (Xarelto®)	Absorption: Rapid Bioavailability: 10 mg dose: ~80-100% 20 mg dose: ~66%	Vd: ~50 L Protein binding: ~92% to 95% (primarily to albumin)	5-9 hours *elderly: 11-13 hours	2-4 hours	Hepatic via CYP3A4/5 and CYP2J2	Urine (66%; 36% as unchanged drug and 30% as inactive metabolites); feces (28%; 7% as unchanged drug and 21% as inactive metabolites)

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2013), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and

indexed on MEDLINE prior to 4/2013, evaluating efficacy of the factor Xa inhibitors are included. Trials evaluating the factor Xa inhibitors as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded. The following reports were excluded (note: some were excluded for more than 1 reason):

- Individual clinical trials which evaluated pharmacokinetic studies, utility studies[25], or cost analyses.
- Individual trials comparing the factor Xa inhibitors in indirect comparison analyses[26-29], dose-finding studies or in indications other than the approved indications for the agent.[30]
- Individual clinical trials evaluating the factor Xa inhibitors or formulations not currently available in the US or clinical trials without access to the full article.

Clinical Efficacy

The factor Xa inhibitors are not directly compared in any clinical trials. A number of trials are available comparing the factor Xa inhibitors to warfarin, enoxaparin, aspirin, or placebo. A brief summary of this clinical evidence is provided below. See table 5 for a summary of the available clinical data evaluating the two new oral factor Xa inhibitors.

Apixaban is indicated in the prevention of stroke or embolism in patients with nonvalvular atrial fibrillation (AF). Two trials evaluating apixaban in patients with AF are available. Connolly et al[31] studied 5,599 patients randomized to receive apixaban or aspirin in a comparative clinical trial lasting just over one year. Granger at al[32] studied 18,201 patients randomized to receive apixaban or warfarin in a comparative clinical trial lasting nearly two years. Results from both trials demonstrated significantly reduced rates of stroke with apixaban therapy compared to both aspirin and warfarin therapies with similar or reduced rates of bleeding adverse events. Apixaban therapy was also evaluated in the prophylaxis of DVT or PE in patients undergoing major surgery or with a recent history of DVT/PE in 5 additional trials. Four of the trials compared apixaban to enoxaparin in patients undergoing hip or knee surgery.[33-36] Two trials found superiority for apixaban in reducing VTE and all-cause mortality with no differences in bleeding rates between the treatment groups.[35, 36] Two trials found no differences in efficacy between the agents.[33, 34] The final trial compared apixaban to placebo in patients receiving up to 12 additional months of prophylactic therapy and found a greater reduction in recurrent VTE without an increase in bleeding events in the apixaban treatment group compared to placebo.[37] See table 5 for a summary of these clinical trials.

Rivaroxaban is indicated in the prevention of stroke or embolism in patients with nonvalvular atrial fibrillation (AF) and in the prevention or treatment of DVT/PE. One trial evaluating rivaroxaban therapy in patients with AF is available for evaluation. Patel et al[38] evaluated 14,2647 patients who were randomized to receive warfarin or rivaroxaban for 590 days and found rivaroxaban therapy to be noninferior to warfarin in reducing rate of stroke with similar rates of bleeding events. Three trials evaluating the efficacy of rivaroxaban therapy in the treatment of VTE are available for evaluation. Bauersachs et al[39] evaluated 3,449 patients with a DVT randomized to receive warfarin or rivaroxaban for up to 12 months and found no

differences in the rate of recurrent VTE or bleeding between the treatment groups. Romualdi et al[40] evaluated 1,197 patients randomized to receive rivaroxaban or placebo in patients with VTE for up to 12 months and found a significantly reduced rate of recurrent VTE in patients receiving rivaroxaban compared to those receiving placebo with no differences in bleeding adverse events between treatment groups. Büller[41] et al evaluated 4,832 patients randomized to receive rivaroxaban or placebo in patients with PE for up to 12 months and found no differences in the rate of recurrent VTE or bleeding between the treatment groups. Four trials evaluating the efficacy of rivaroxaban in the prevention of VTE are available for evaluation.[42-45] Two trials compared rivaroxaban to enoxaparin in the prevention of VTE in patients undergoing total hip replacement and found significantly reduced rates of DVT, PE and death in patients taking rivaroxaban compared to enoxaparin.[42, 43] Two trials compared rivaroxaban to enoxaparin in patients undergoing total knew replacement and found similarly significantly reduced rates of VTE and death with rivaroxaban therapy compared to enoxaparin therapy.[42-45] No differences in bleeding events were reported between treatment groups in all four trials. See table 5 for a summary of these clinical trials.

Table 5. Summary of Clinical Evidence Evaluating the Oral Factor Xa Inhibitors[46]

Trial	N	Patient population	Comparator	Outcomes
Apixaban				
ADVANCE-1[34]	3,195	Patients undergoing TKR	Enoxaparin 30 mg bid x 10-14 days	Did not meet noninferiority; significant reduction in bleeding
ADVANCE-2[35]	3,057	Patients undergoing TKR	Enoxaparin 40 mg daily x 10-14 days	Superior for VTE and all-cause mortality; similar bleeding rates
ADVANCE-3[36]	5,407	Patients undergoing THR	Enoxaparin 40 mg daily x 32-38 days	Superior for VTE and all-cause mortality; similar bleeding rates
ADOPT[33]	6,528	Patients hospitalized with medical illness	Enoxaparin 40 mg daily x 30 days	No differences in death from VTE, PE, DVT; increased bleeding with apixaban
AMPLIFY-EXT[37]	2,486	Patients with VTE	Placebo x 6-12 months	Superior for VTE; similar bleeding rates
AVERROES[31]	5,599	Patients with AF	Aspirin for 1.1 years	Superior for reducing stroke; similar adverse event rates
ARISTOTLE[32, 46]	18,201	Patients with AF	Warfarin for 1.8 years	Superior for preventing stroke; decreased bleeding
Rivaroxaban				
RECORD 1[42]	4,541	Patients undergoing THR	Enoxaparin 40 mg daily x 30-42 days	Superior for rate of DVT, PE and death; similar bleeding rates
RECORD 2[43]	2,509	Patients undergoing THR	Enoxaparin 40 mg daily x 30-42 days	Superior for rate of DVT, PE and death; similar bleeding rates
RECORD 3[44]	2,556	Patients undergoing TKR	Enoxaparin 40 mg daily x 13-17 days	Superior for rate of DVT, PE and death; similar bleeding rates
RECORD 4[45]	3,148	Patients undergoing TKR	Enoxaparin 30 mg twice daily x up to 17 days	Superior for rate of DVT, PE and death; similar bleeding rates

MAGELLAN[47]	8,101	Patients hospitalized with medical illness	Enoxaparin 40 mg daily x 10-14 days, 31-39 days	Noninferior at 1-14 days; Superior for DVT, PE, death at 31-39 days; increased bleeding rate
EINSTEIN-DVT[39]	3,449	Patients with DVT	Warfarin x 3, 6, 12 months	No differences in VTE or bleeding
EINSTEIN-Extension[40]	1,197	Patients with VTE	Placebo x 6, 12 months	Superior for rate of VTE; no differences in bleeding
EINSTEIN-PE[41]	4,832	Patients with PE	Placebo x 3, 6, 12 months	No differences in VTE or bleeding
ROCKET-AF[38]	14,264	Patients with AF	Warfarin x 590 days with 707 days of follow-up	Noninferior in reducing stroke; similar bleeding rates

Key: TKA = total knee replacement, THP = total hip replacement, DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venous thromboembolism, AF = atrial fibrillation

Fondaparinux is indicated in the treatment or prophylaxis of DVT and PE. Fondaparinux therapy is compared to LMWH or placebo in many trials. A meta-analysis of four randomized, controlled trials (n = 7344) comparing fondaparinux to enoxaparin in patients undergoing hip or knee surgery is available.[48, 49] Evaluation of the trials found a significantly greater reduction in the incidence of VTE in the enoxaparin group compared to the fondaparinux group. The overall incidence of bleeding events was low and did not differ between the treatment groups. Safety and efficacy of fondaparinux was consistent across all surgery types and subgroups. A pharmacoeconomic analysis of the four trials found the reduction in incidence of VTE with prophylactic fondaparinux is associated with lower costs in patients who undergo major hip or knee surgery compared with enoxaparin.[50, 51] A meta-analysis evaluating the safety of fondaparinux is also available. Eikelboom et al[51] identified 8 clinical trials, totaling 13,085 patients, comparing fondaparinux with either LMWH or placebo for the prophylaxis of venous thromboembolism in patients hospitalized for surgical or medical reasons. According to the data, fondaparinux is not associated with increased risk of bleeding compared to LMWH or placebo. In general, the authors found a major bleeding event is a strong predictor of mortality in all patients hospitalized and receiving VTE prophylaxis.

The majority of the comparative clinical trials evaluating the factor Xa inhibitors demonstrate superiority for apixaban, rivaroxaban or fondaparinux compared to other anticoagulant agents (warfarin, enoxaparin, aspirin). Safety appears to be similar across treatment groups. Many meta-analyses and systematic reviews evaluating the newer oral anticoagulants (dabigatran, rivaroxaban, apixaban) are available. In general, results from these trials suggest the newer agents are similar in safety and efficacy compared to each other and to the older anticoagulants (warfarin, enoxaparin).[26-28, 52-55] Overall, statistical differences in safety or efficacy reported in the clinical trials and meta-analyses evaluating the factor Xa inhibitors were clinically similar.

Adverse Drug Reactions

The factor Xa inhibitors are generally well tolerated. The most common adverse event associated with factor Xa inhibitors is bleeding.[4, 5] Clinical trials comparing the factor Xa inhibitors to enoxaparin, warfarin, or aspirin found similar rates of bleeding adverse events between treatment groups. Apixaban and rivaroxaban have a black box warning for an increased risk of stroke upon discontinuation of therapy in patients with atrial fibrillation. Fondaparinux and rivaroxaban have a black box warning for concomitant use with neuraxial anesthesia and the increased risk for developing epidural or spinal hematomas. There is no specific reversal agent for the factor Xa inhibitors.[4, 5] Table 6 lists the adverse events of the factor Xa inhibitors reported in the package inserts.

Table 6. Adverse Events Reported with the Factor Xa Inhibitors[1-5]

Adverse Event	Apixaban (Eliquis®; %)	Fondaparinux (Arixtra®; %)	Rivaroxaban (Xarelto®; %)
Bleeding event			
Any bleed	5-12	2-4	5-21
Major bleed	≤2	1-3	1-6
Other adverse events			
Anemia	3	1-20	<1
Bruising	1	1	3
Fever	NR	4-14	1-3
Increased liver enzymes	1	2-3	<1
Injection site reaction	--	1-10	--
Nausea	3	3-11	1-3
Thrombocytopenia	NR	3	<1

Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive.
NR = not reported

Summary

Anticoagulation is recommended in the treatment and prevention of venous thromboembolism (VTE) in patients with a history of VTE or in patients undergoing major surgery. Anticoagulation is also recommended in the prevention of stroke or embolism in patients with nonvalvular atrial fibrillation (AF). Many anticoagulant drug therapies are currently available for use in the United States. The factor Xa inhibitors are among this group and three agents are currently available for use in the United States: apixaban, fondaparinux, and rivaroxaban. Apixaban and rivaroxaban are available as oral tablets and fondaparinux is a subcutaneous injection. Apixaban is dosed twice daily and rivaroxaban should be taken with food. Labeled indications vary between the agents. The American Heart Association and American Stroke Association recommended the use of an anticoagulant to prevent stroke in patients with AF and list apixaban and rivaroxaban as efficacious alternatives to warfarin or aspirin in patients requiring anticoagulation for stroke prevention. The American College of Chest Physicians recommend a low-molecular-weight heparin (LMWH) for DVT/PE

prophylaxis in patients undergoing hip or knee replacement surgery. Apixaban, fondaparinux, and rivaroxaban are listed as alternatives. The guidelines recommend initial therapy with a parenteral anticoagulant (preferably LMWH or fondaparinux) followed by VKA for *treatment* of a DVT of the leg or PE.

The factor Xa inhibitors are not directly compared in any clinical trials. A number of trials comparing the factor Xa inhibitors to warfarin, enoxaparin, aspirin, or placebo are available for evaluation. The majority of this comparative clinical evidence suggests noninferiority or superiority for apixaban, rivaroxaban or fondaparinux compared to the other anticoagulant agents. Safety appears to be similar across treatment groups. Statistical differences in safety or efficacy reported in the clinical trials were clinically similar. Factor Xa inhibitor therapy is well tolerated and the most common adverse event reported with the agents is bleeding. Black box warnings for increased risk of stroke upon discontinuation of therapy and increased risk for developing epidural or spinal hematomas with concurrent spinal anesthesia are listed with the factor Xa inhibitors. There is no specific reversal agent for the factor Xa inhibitors. Overall, selection of an anticoagulant therapy or factor Xa inhibitor should be based on labeled indications and patient specific characteristics (age, weight, comorbidities, etc.).

References

1. GlaxoSmithKline. Arixtra (fondaparinux) injectable solution [package insert]. In. Research Triangle Park, NC GlaxoSmithKline 2011.
2. Bristol-Myers Squibb. Eliquis (apixaban) oral tablets [package insert]. In. Princeton, New Jersey: Bristol-Myers Squibb Company and Pfizer Inc; 2012.
3. Janssen Pharmaceuticals. Xarelto (rivaroxaban) oral tablets [package insert]. In. Titusville, NJ: Janssen Pharmaceuticals, Inc. and Bayer HealthCare; 2011.
4. AHFS Drug Information, ed. AHFS 2013 Drug Information. Bethesda, MD: American Society of Health-System Pharmacists; 2013.
5. Lexi-Comp I, ed. Drug Information Handbook. 21st ed. Hudson, OH: Lexi-Comp; 2013.
6. Wilson PW. Prediction of cardiovascular disease events. Cardiol Clin;29:1-13.
7. Srikanth S, Deedwania P. Primary and secondary prevention strategy for cardiovascular disease in diabetes mellitus. Cardiol Clin;29:47-70.
8. Lardizabal JA, Deedwania P. Lipid-lowering therapy with statins for the primary and secondary prevention of cardiovascular disease. Cardiol Clin;29:87-103.
9. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation;123:933-44.
10. Gupta R, Deedwania P. Interventions for cardiovascular disease prevention. Cardiol Clin;29:15-34.
11. Franco M, Cooper RS, Bilal U, Fuster V. Challenges and opportunities for cardiovascular disease prevention. Am J Med;124:95-102.
12. Ketchum K, Peterson K, Thakurta S, Low A, McDonagh MS. Drug class review: Newer Antiplatelet Agents. Update 2. In: Oregon Health and Science University; 2011.
13. De Lemos JA, O'Rourke RA, Harrington R. Chapter 59. Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction. In: Fuster V, Walsh RA, Harrington RA, eds. Hurst's the heart. 13th ed. New York: McGraw-Hill; 2011.
14. Weitz JI. Chapter 30. Blood Coagulation and Anticoagulant, Fibrinolytic, and Antiplatelet Drugs. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill; 2011.
15. Weitz JI. Chapter 118. Antiplatelet, Anticoagulant, and Fibrinolytic Drugs. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medecine. 18th ed. New York: McGraw-Hill; 2012.
16. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest;141:e44S-88S.
17. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol;57:e101-98.
18. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation;123:e269-367.
19. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace 2006;8:651-745.
20. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest;141:e531S-75S.

21. Furie KL, Goldstein LB, Albers GW, et al. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. Stroke;43:3442-53.
22. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest;141:e278S-325S.
23. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest;141:7S-47S.
24. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:454S-545S.
25. Carter KL, Streiff MB, Ross PA, et al. Analysis of the projected utility of dabigatran, rivaroxaban, and apixaban and their future impact on existing Hematology and Cardiology Anticoagulation Clinics at The Johns Hopkins Hospital. J Thromb Thrombolysis;34:437-45.
26. Rasmussen LH, Larsen TB, Graungaard T, Skjoth F, Lip GY. Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. BMJ;345:e7097.
27. Schneeweiss S, Gagne JJ, Patrick AR, Choudhry NK, Avorn J. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes;5:480-6.
28. Testa L, Agnifili M, Latini RA, et al. Adjusted indirect comparison of new oral anticoagulants for stroke prevention in atrial fibrillation. QJM;105:949-57.
29. Gomez-Outes A, Terleira-Fernandez AI, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. BMJ;344:e3675.
30. Nieto JA, Espada NG, Merino RG, Gonzalez TC. Dabigatran, rivaroxaban and apixaban versus enoxaparin for thomboprophylaxis after total knee or hip arthroplasty: pool-analysis of phase III randomized clinical trials. Thromb Res;130:183-91.
31. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med;364:806-17.
32. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med;365:981-92.
33. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med;365:2167-77.
34. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med;363:2487-98.
35. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet;375:807-15.
36. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med 2009;361:594-604.
37. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med;368:699-708.
38. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med;365:883-91.
39. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med;363:2499-510.
40. Romualdi E, Donadini MP, Ageno W. Oral rivaroxaban after symptomatic venous thromboembolism: the continued treatment study (EINSTEIN-extension study). Expert Rev Cardiovasc Ther;9:841-4.
41. Buller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med;366:1287-97.
42. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008;358:2765-75.
43. Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008;372:31-9.
44. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008;358:2776-86.

45. Turpie AG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009;373:1673-80.
46. King CS, Holley AB, Moores LK. Moving toward a more ideal anticoagulant: the oral direct thrombin and factor xa inhibitors. Chest;143:1106-16.
47. Cohen AT, Spiro TE, Buller HR, et al. Extended-duration rivaroxaban thromboprophylaxis in acutely ill medical patients: MAGELLAN study protocol. J Thromb Thrombolysis;31:407-16.
48. Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med 2002;162:1833-40.
49. Turpie AG, Eriksson BI, Lassen MR, Bauer KA. A meta-analysis of fondaparinux versus enoxaparin in the prevention of venous thromboembolism after major orthopaedic surgery. J South Orthop Assoc 2002;11:182-8.
50. Dranitsaris G, Kahn SR, Stumpo C, et al. Pharmacoeconomic analysis of fondaparinux versus enoxaparin for the prevention of thromboembolic events in orthopedic surgery patients. Am J Cardiovasc Drugs 2004;4:325-33.
51. Eikelboom JW, Quinlan DJ, O'Donnell M. Major bleeding, mortality, and efficacy of fondaparinux in venous thromboembolism prevention trials. Circulation 2009;120:2006-11.
52. Cohen A, Drost P, Marchant N, et al. The efficacy and safety of pharmacological prophylaxis of venous thromboembolism following elective knee or hip replacement: systematic review and network meta-analysis. Clin Appl Thromb Hemost;18:611-27.
53. Harenberg J, Marx S, Diener HC, et al. Comparison of efficacy and safety of dabigatran, rivaroxaban and apixaban in patients with atrial fibrillation using network meta-analysis. Int Angiol;31:330-9.
54. Li XM, Sun SG, Zhang WD. Apixaban versus enoxaparin for thromboprophylaxis after total hip or knee arthroplasty: a meta-analysis of randomized controlled trials. Chin Med J (Engl);125:2339-45.
55. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol;110:453-60.